Chemical Emulation of the Biosynthetic Route to Glycinoeclepin from a Cycloartenol Derivative

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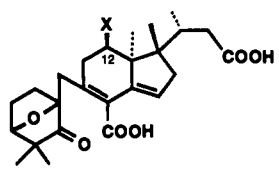
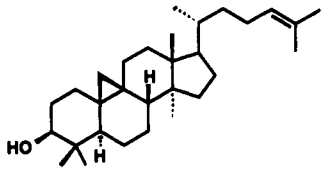
Glycinoeclepin (**1**) is one of the most notable of recently discovered plant natural products for a multitude of reasons, including: (1) its probable bioregulatory function in the commercially important soybean plant; (2) secretion from the plant root into the soil, where it stimulates hatching of dormant eggs of the predatory nematode *Heterodera glycines* at *ca.* 10^{-12} g/mL; (3) potential utility in agriculture as an antinematodic agent; (4) its unusual biosynthesis, presumably from the plant sterol cycloartenol (**2**);[1] and (5) the novelty of its structure. The current



1, X = OH
4, X = H



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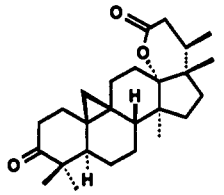
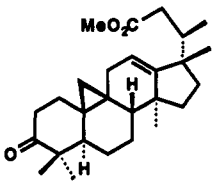
high level of interest in glycinoeclepin is reflected in the rapid development of three different total syntheses.[2] The emulation of the complex biosynthesis of **1** in a chemical way poses a unique challenge to synthesis because of the extensive structural changes which are involved, including rearrangements of carbon and carbon–carbon cleavages, and the high degree of chemical selectivity and control which are required. A priori, an additional obstacle is the lack of availability of cycloartenol and the majority of its many known derivatives, which, though ubiquitous in plants, are usually found in very small amounts. A striking exception is the spiro lactone abietospiran (**3**), which constitutes *ca.* 1% of the bark of the common white fir tree, *Abies alba*,[3] and which is potentially cheap and available in multiton quantities since vast amounts of this bark are generated each year as waste by the logging industry. We describe herein a synthesis of 12-desoxyglycinoeclepin (**4**) from abietospiran by a route which depends on a number of highly selective and/or novel steps but which utilizes relatively simple and inexpensive reagents.

The first stage of the synthesis of **4** (Scheme 1), which involves selective dissection of the C(17) side chain and removal of four carbons, was accomplished by sequential α-hydroxylation, mesylate formation, elimination to **5**, and Lemieux–Rudloff oxidation[4] to **6** in 60% overall yield. A variety of experiments to effect the conversion of the 26-hydroxy derivative of **3** to **6** in a single step resulted generally in only 20% yield of **6** (with CrO_3–HOAc as reagent). The keto lactone **7**, which was obtained from **6** by a highly selective catalytic RuO_4 oxidative cleavage reaction,[5] underwent C(17) cation formation and double methyl group migration to form **8** stereospecifically. This interesting reaction proceeds in stages: (1) rearrangement of methyl from C(13) to C(17) with formation of a δ-lactone (**7a**) (BF_3·Et_2O at 0 °C) and (2) rearrangement of methyl from C(14) to C(13) during slow addition of H_2O at 0 °C. (The intermediate δ-lactone **7a** has



7a



7b

been isolated from the reaction with BF_3·Et_2O alone using Et_3N quench and extractive isolation.) Selective dehydrogenation of **8** to form diene **10** was effected via epoxide **9** under carefully controlled and very mildly acidic conditions. Stereospecific reduction of the 3-keto group to form **11** and selective epoxidation of the more reactive 7,8-double bond of **11** gave epoxy alcohol **12** efficiently. Exposure of **12** to BF_3·Et_2O at −20 °C resulted in cyclopropylcarbinyl cation formation, C(9)–C(10) cleavage, and oxygen bridging from C(3) to C(10) to produce **13** in a single step, which may be a close mimic of the biosynthetic process. Dess–Martin oxidation of **13**[6] to the corresponding ketone and Rubottom oxidation[7] provided α-hydroxy ketone **16**, which was oxidized and esterified to seco ester aldehyde **17**, thereby establishing the topology of glycinoeclepin. The replacement of the C(5) formyl group of **17** by a carbonyl function could not be accomplished by a variety of oxidation procedures based on prior conversion of the aldehyde function to enol, enolate, or enamine intermediates, due to a combination of extreme steric hindrance and sensitivity to β-elimination of the C(3)–C(10) oxygen bridge. Therefore, a special strategy was devised using an intermediate *N*-hydroxy-2-thiopyridone (Barton) ester (**19**) of the acid **18** (from chlorite oxidation[8] of aldehyde **17**).[9] Irradiation of **19** with a sunlamp in the presence of O_2 resulted in decarboxylation to the C(5) radical, which was trapped by O_2 to give the 5-hydroperoxide, reduction of which by Ph_3P gave the hydroxy diester **20**. Dess–Martin oxidation of **20** afforded 12-desoxyglycinoeclepin dimethyl ester **21**, which was identical with an authentic sample[10] by IR, NMR, MS, and chromatographic comparison. Saponification of the dimethyl ester **21** (1:1 dimethoxyethane–1 M aqueous lithium hydroxide at 46 °C for 36 h) afforded a sample of 12-desoxyglycinoeclepin (**4**) for biological studies.

Modification of the above process to allow the synthesis of glycinoeclepin should also be possible by taking advantage of intermediate **7a** and the related unsaturated ester **7b**, since epoxidation of **7b** and rearrangement[2c] would lead to introduction of the 12β-hydroxyl function of **1**. It is also of interest to determine whether some of the intermediates in the above synthesis of **4** from **3** are naturally occurring compounds.[11]

Supplementary Material Available: Experimental and characterization data for the new compounds described herein (21

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(9) Barton, D. H. R.; Crich, D.; Motherwell, W. B. *J. Chem. Soc., Chem. Commun.* **1983**, 939–940. In our work, the Barton ester **19** was prepared by the reaction of the triethylammonium salt of **18** with bis(2-oxo-3-oxazolidinyl)-phosphonic chloride (BOPCl) for a few minutes to form the corresponding mixed anhydride and subsequent reaction with *N*-hydroxy-2-thiopyridone.

(10) Prepared from glycinoeclepin dimethyl ester by conversion to the pentafluorophenoxy thioformate ester and heating in the presence of Bu_3SnH and AIBN.

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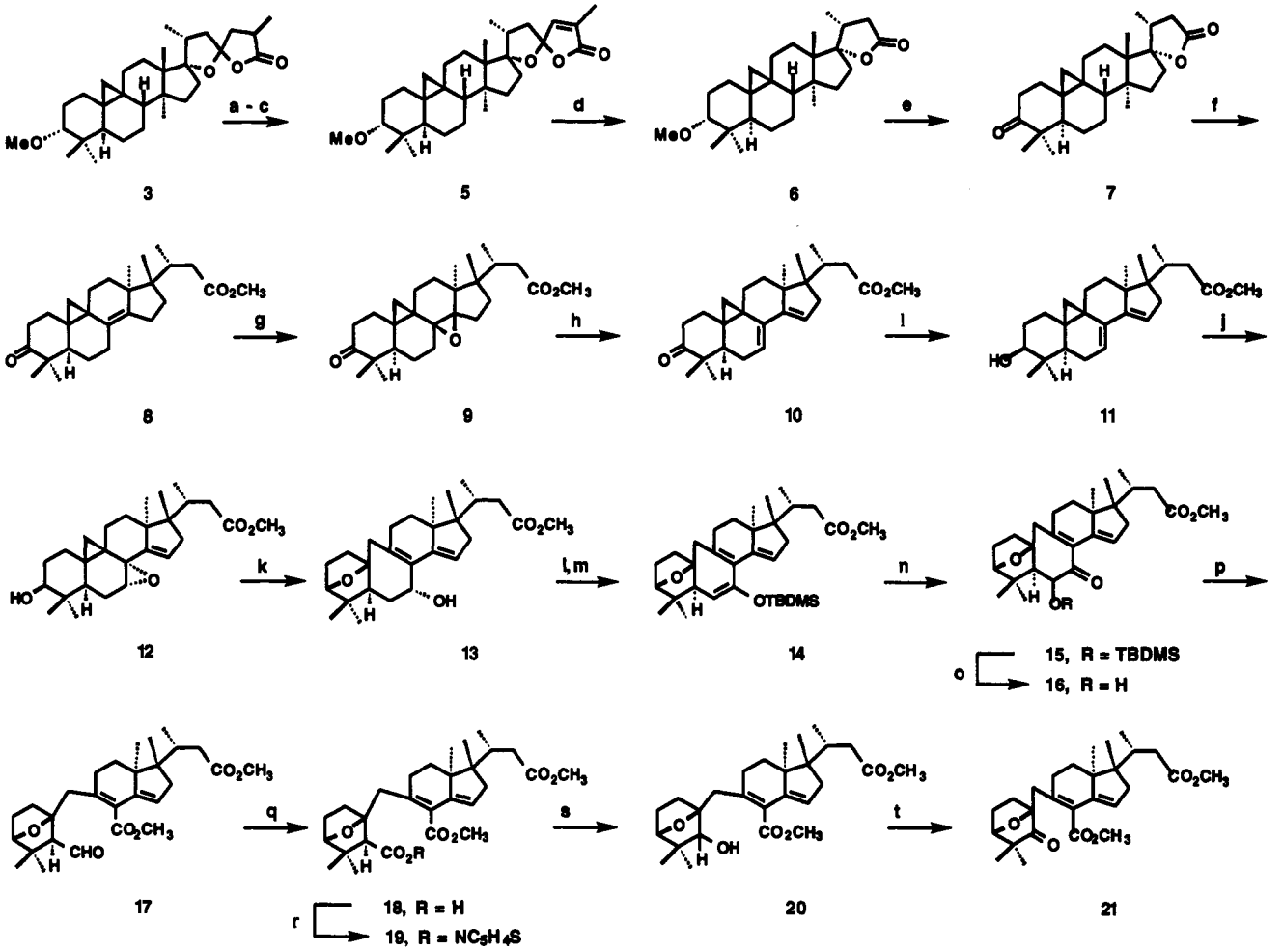
Scheme 1[a]



[a] (a) (1) LDA, THF at −78 °C; O_2; (2) Me_2S; 90%; (b) excess MsCl, Et_3N, CH_2Cl_2, 23 °C; 87%; (c) excess DBU, C_6H_6, reflux, 12 h; 90%; (d) catalyst $KMnO_4$, $NaIO_4$, *t*-BuOH, H_2O, 1 h; 85%; (e) $RuCl_3 \cdot (H_2O)_x$, CCl_4–CH_3CN–H_2O (1:1:1), 8 h; 65%; (f) (1) 6 equiv of $BF_3 \cdot OEt_2$, CH_2Cl_2–hexane (5:2), 1 h, 0 °C; 11 equiv of H_2O gradually over 30 min, 0 °C; (2) CH_2N_2, CH_2Cl_2, 72%; (g) 1.1 equiv of MCPBA, 23 °C, CH_2Cl_2; 81%; (h) catalyst $MgSO_4$, silica gel, 23 °C, $CHCl_3$, 2–4 h; 66%; (i) $NaBH_4$, EtOH–THF (5:2), −40 °C; 96%; (j) 1 equiv of MCPBA, 23 °C, CH_2Cl_2; 85%; (k) 2 equiv of $BF_3 \cdot OEt_2$, CH_2Cl_2, −20 °C; 60%; (l) Dess–Martin reagent, pyridine, 23 °C, CH_2Cl_2; 80%; (m) LiHMDS, TBDMSOTf, THF, −78 °C; 92%; (n) 1 equiv of MCPBA, CH_2Cl_2, 23 °C; 83%; (o) HF–CH_3CN (1:10), 10 h; 90%; (p) $Pb(OAc)_4$, MeOH–C_6H_6 (1:2), 30 min, 23 °C; 82%; (q) $NaClO_2$, *t*-BuOH, 2-methyl-2-butene, NaH_2PO_4, 23 °C; 84%; (r) (1) BOPCl, Et_3N, THF, 23 °C; (2) $HONC_4H_4S$, 12 h, 23 °C; (s) (1) *hν*, −10 °C, THF, O_2, 10 min; (2) Ph_3P; (t) Dess–Martin reagent, pyridine, 23 °C, CH_2Cl_2; 40% for four steps.

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